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PHASE-TRANSFER CATALYSIS: A GENERAL METHOD OF METHOXYMETHYLATION OF THE HYDROXYL FUNCTION

F.R. van Heerden, J.J. van Zyl, G.J.H. Rall,* E.V. Brandt and D.G. Roux

Department of Chemistry, University of the Orange Free State, P.O. Box
339, Bloemfontein, 9300 Rep. of South Africa

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Many natural flavonoids, the majority of which are derived biogenetically from substituted 2'-hydroxychalcones, exhibit physiological activity. Amongst these are phytoalexins, insecticides, fish poisons, and potential anti-cancer drugs, while others show oestrogenic activity.

Their synthesis invariably proceeds *via* complex chalcones, involving appropriate protection of hydroxyl function as an indispensable prerequirement for condensations, rearrangements of substituents and their introduction. Application of the β-methoxyethoxymethyl-[1] and methoxymethyl groups[2,3,4] received much attention as excellent results were reported, while deprotection was accomplished with mild acids[1,2]. Initial salt formation, however, is a prerequisite in both methods. This poses problems with compounds (1) [required as intermediate in the syntheses of sericone (9) and related compounds[5]], (3), (5) and (7) which resist salt formation and isolation as such, in the anhydrous form.

We hereby demonstrate a high-yield conversion of phenols to their methoxymethyl ethers which should find general application. A mixture of an appropriate phenol (1 mmol in CH_2Cl_2) and sodium hydroxide (1-2 mmol in water) is stirred at room temperature for 20 minutes in the presence of 0.1-0.2 mmol phase-transfer catalyst[6] (Adogen 464 from Aldrich). Chlorodimethyl ether is added until reaction is complete (a three- to fivefold excess is normally required). The reaction is fast and complete within 25 minutes in the above-mentioned cases. The aqueous phase is separated and extracted with dichloromethane (2x). The combined organic extract is dried (Na_2SO_4), evaporated to dryness, and separated from the Adogen on a silica gel column with an appropriate eluent (Table). Evaporation gives the methoxymethyl derivatives in excellent yield (Table). Other examples are the conversion of resacetophenone (95%) and *p*-hydroxybenzaldehyde (92%) into their respective methoxymethyl derivatives.

The principal advantages of this method are that in contrast to the strictly anhydrous[2,4] and inert conditions[2,7] and stoichiometric amounts of chlorodimethyl ether[7] of previous procedures, reaction may now be executed in aqueous medium with almost quantitative yields. Reaction times are also reduced by *ca.* 60-70%.

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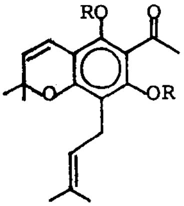
TABLE

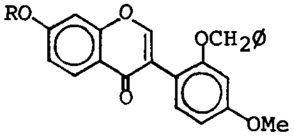
Phenol	Methoxymethyl ether*	Yield(%)	Eluent≠	R_F
1	2	79	H:A (8:2)	0.61
3	4	95	B:A (95:5)	0.35
5	6	91	B:A (7:3)	0.53
7	8	86	H:A (8:2)	0.40

* Satisfactory m.s. and ^{1}H-n.m.r. spectra were obtained

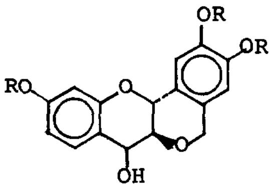
≠ A = acetone; B = benzene; H = hexane



(1) R=H (2) R=CH_2OCH_3

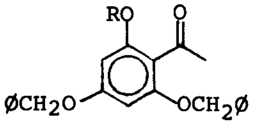


(3) R=H (4) R=CH_2OCH_3



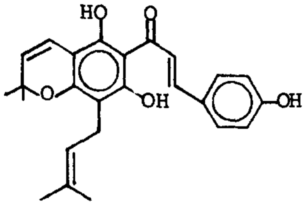
(5) R=H

(6) R=CH_2OCH_3



(7) R=H

(8) R=CH_2OCH_3



(9)

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